

## **REMARKS**

### **Preliminary Remarks**

This response is timely filed, as it is being filed with a petition for a one-month extension of time to respond. After entry of this amendment, claims 12-27 will be pending in this patent application. The applicants have cancelled claims 1-11 without prejudice, have amended claims 14 and 16 to broaden them and to make various editorial changes, and have added new claims 18-27. In addition to the claim amendments, the applicants have made editorial changes to the specification, and have made an editorial change to the drawings by way of a replacement sheet including Figure 5. The applicants do not believe that any new matter has been introduced by these amendments.

### **Patentability Remarks**

#### **35 U.S.C. § 112**

Claims 15 and 16 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The examiner's position is that certain words and phrases in those claims, particularly "noise" in claim 15 and "uninformative probes" and "one cut-off threshold" in claim 16, render them indefinite.<sup>1</sup> The applicants respectfully disagree with the examiner's position.

On the contrary, the applicants respectfully submit that each and every one of the phrases cited by the examiner is clear and definite when read in view of the specification. Therefore, the applicants respectfully request that the examiner reconsider the rejection after reviewing at least the portions of the specification in which those terms are explicitly defined or used contextually so as to establish a definition. Although the applicants believe that the cited terms should be read and defined in view of the entire specification, the applicants submit that paragraphs [0041] and [0044] may be particularly helpful to the examiner.

The applicants note two well-known precepts of patent law: first, that claim terms should be given their broadest reasonable interpretation consistent with both the specification and the interpretation that skilled artisans would reach; and, second, that a patent applicant has a right to be his or her own lexicographer and to create terms appropriate to the invention when necessary. See, for example, MPEP §§ 2111 and 2111.01, where those precepts and their interplay are explained, and some of the voluminous case law relating to them is cited.

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<sup>1</sup> The applicants note that the amendments made to claim 16 are irrelevant to the substance of this rejection.

With those two precepts in mind, the applicants respectfully submit that the examiner appears to be imputing indefiniteness in claims 15 and 16 where none exists. For example, the applicants note the examiner's proposed construction of the term "threshold" to mean "a piece of wood or stone placed beneath a door." As the applicants noted above, that term is defined in the specification. Even if it was not, the construction the examiner proposes is clearly contrary to the art-based plain meaning of the term. A skilled artisan, when reading the applicants' claims, would not confuse "a piece of wood or stone placed beneath a door" with the sort of threshold the applicants are claiming.

Accordingly, the applicants respectfully request that the rejection be withdrawn and not extended to any of the new claims.

35 U.S.C. § 101

Claims 1-11 were rejected under 35 U.S.C. § 101 as allegedly being directed to non-statutory subject matter. The applicants have cancelled those claims without prejudice; therefore, the rejection is moot and should be withdrawn. Additionally, the applicants respectfully submit that the rejection should not be extended to the new claims.

35 U.S.C. § 102

Claims 1-15 and 17 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Schena *et al.*, "Parallel human genome analysis: Microarray-based expression monitoring of 1000 genes," 10614 *Proc. Natl. Acad. Sci.* 93 (1996) (hereinafter "the Schena article"). The applicants note that the rejection is moot with respect to cancelled claims 1-11 and should be withdrawn, but will respond with respect to pending independent claim 12 and pending dependent claims 13-15 and 17.

The examiner's position is that the Schena article discloses "a system and method for predicting splicing transcripts using DNA chip expression data (EST) wherein differential expression data are derived from microarrays containing human cDNAs." The examiner cites Benson *et al.*, "GenBank," 25 *Nucleic Acids Research* 1 (1997) and Schuler, "Pieces of the puzzle: expressed sequence tags and the catalog of human genes," 75 *J. Mol. Med.* 694 (1997) (hereinafter "the Benson article" and "the Schuler article," respectively) to "expand on the disclosure" of the Schena article. The applicants respectfully disagree with the examiner's position and with the manner in which the rejection was made.

“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (emphasis added).

Before delving into the merits of the rejection, the applicants respectfully submit that the examiner’s use of and reliance on the Schuler and Benson articles is improper, and that the rejection should be withdrawn for at least that reason. As stated above, anticipation requires that the elements of a claim be found in a single reference. While it may be proper in some circumstances to rely on a secondary non-prior art reference in an anticipation rejection merely to define a term found in the applied prior art reference, the applicants submit that the examiner has gone beyond that standard in making the present rejection. As stated by the examiner, the purpose for citing the Schuler and Benson articles is to “expand on the disclosure” of the Schena reference, which is not a proper use of a secondary reference in an anticipation rejection. Nonetheless, in order to expedite prosecution, the applicants will respond to the rejection, and will explain below in more detail why the use of the Schuler and Benson articles is improper.

Independent claim 12 recites “a method for predicting alternative splicing transcripts using DNA chip expression data.” Among other things, the method includes the task of “performing a first splice variant prediction to produce first splice variant prediction data.” The applicants note that nowhere in the official action has the examiner explained where “performing a first splice variant prediction” is disclosed in the Schena article. Moreover, the applicants respectfully submit that no such disclosure is present in the Schena article, because the Schena article is actually directed to a completely different process.

The Schena article discloses a process for investigating the effects of heat shock and phorbol ester treatment on gene expression in human peripheral blood lymphocytes using DNA chip techniques. There is no disclosure or suggestion of a method for predicting alternative splicing transcripts, and no part of the Schena article relates to making such predictions. Rather, the examiner’s belief that the Schena article reads on claim 12 is apparently based on the assertion that the mere mention of expressed sequence tags in relation to the process disclosed by the Schena article constitutes making splice variant predictions. The applicants respectfully disagree with that assertion.

As the applicants noted briefly above, large portions of the examiner’s argument appear to rest on the teachings in the Schuler article. For example, in support of the assertion

that expressed sequence tags are used “for predicting alternative splicing transcripts,” the examiner offers only a passage from the Schuler article (p. 695, col. 3), which states that “the possibility of alternative splicing patterns adds a new level of complexity to the problem. On top of this, some clones are derived from partially spliced pre-mRNAs, which are nearly indistinguishable from true splicing variants” (emphasis added). Thus, the rejection and the argument in support of it are clearly, and improperly, based, at least in part, on the Schuler article.

However, merely to clarify the record, the applicants respectfully submit that the examiner has misconstrued the Schuler reference. In particular, while the examiner quotes the above passage as evidence that expressed sequence tags may be used to predict alternative splicing transcripts, the applicants submit that it actually points out the opposite – that the very nature of expressed sequence tags makes it difficult to appreciate or predict whether a possible splice variant observed in an expressed sequence tag is a true splice variant or an artifact resulting from the nature of the expressed sequence tag itself. In other words, the Schuler article appears to do nothing more than explain the difficulty of predicting alternative splicing transcripts.

Moreover, in the Schena article, the only article whose teachings are relevant to the present 35 U.S.C. § 102 rejection, expressed sequence tags are merely compared to unknown sequences used in the Schena study to determine the identity of those unknown sequences. As the applicants noted above, there is no disclosure or suggestion of a method for predicting alternative splicing transcripts.

Therefore, the applicants respectfully submit that independent claim 12, and the claims that depend from it, are not anticipated by the Schena article. Accordingly, the applicants respectfully request that the rejection be withdrawn and not extended to the new claims. Furthermore, the applicants submit that the new claims are not anticipated for at least the same reasons that were given above with respect to claim 12.

#### 35 U.S.C. § 103

Claims 1-17 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Schena article in view of Eisen *et al.*, “Cluster analysis and display of genome-wide expression patterns,” 95 *Proc. Natl. Acad. Sci.* 14863 (1998) (hereinafter the “Eisen article”). The applicants note that the rejection is moot with respect to cancelled claims 1-11 and

should be withdrawn, but will respond with respect to pending independent claim 12 and pending dependent claims 13-17.

The examiner's position with respect to the Schena article is identical to that set forth above with respect to the 35 U.S.C. § 102(b) rejection. The examiner asserts, particularly with respect to claim 16, that the Eisen article discloses "a method for analyzing cDNA expression data wherein said method comprises a step for generating the log ratio of fluorescence ratio...as in instant claim 16."

Before delving into the merits of the rejection, the applicants note that in paragraph 14 of the official action, the examiner asserts that the Schena article "discloses the limitations to [*sic*; of] claims 1-15 and 17 as discussed above" and gives no further explanation as to how the Schena article or the Eisen article might be relevant to those claims in an obviousness context. If the Schena article anticipates pending claims 12-15 and 17 (an assertion with which the applicants disagree), and there are no further arguments as to how the Schena or Eisen articles might be combined to render those claims obvious, then the applicants submit that claims 12-15 and 17 should not be included in an obviousness rejection.

As to the merits of the rejection, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The applicants respectfully submit that the proposed combination of references does not disclose or suggest all of the features of independent claim 12, or the claims that depend from it. As was explained above with respect to the 35 U.S.C. § 102(b) rejection, the Schena article does not disclose or suggest all of the features of independent claim 12, particularly not the task of "performing a first splice variant prediction to produce first splice variant prediction data." The applicants respectfully submit that the Eisen article does not cure the "defects" of the Schena article.

Furthermore, whatever it may disclose with respect to the use of logarithmic ratios, the Eisen article apparently teaches away from any process that involves predicting splice variants. Specifically, at p. 14864, column 2, 5<sup>th</sup> full paragraph, the Eisen article reads:

We have found repeatedly that genes represented by more than one array element or genes with high degrees of sequence identity are clustered next to, or in the immediate vicinity of, each other. Thus the exact representation of a gene on the array (alternate cDNA clones of differing length in the case of human arrays or homologous genes in *S. cerevisiae*) makes little difference in the observed pattern of gene expression. (Emphasis added.)

Thus, the Eisen article is indicating that any possible splicing variants that might be present can be overlooked in the course of performing the disclosed gene expression monitoring methods, and do not interfere with those methods. Clearly, that passage does not suggest that the method of the Schena article could be modified to include any form of splice variant prediction, and, in fact, appears to suggest the opposite.

Therefore, the applicants submit that claims 12-17 are not rendered obvious by the combination of the Schena and Eisen articles. Accordingly, the applicants respectfully request that the rejection be withdrawn and not extended to the new claims. Furthermore, the applicants submit that the new claims are not rendered obvious for at least the same reasons that were given above.




### III. CONCLUSION

In view of the foregoing, the applicants submit that this application is in condition for allowance. A timely notice to that effect is respectfully requested. If questions relating to patentability remain, the examiner is strongly urged to contact the undersigned at the telephone number set forth below.

Please charge any fees associated with the submission of this paper to Deposit Account Number 033975. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,  
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